WRAMC Practice Guidelines for Therapeutic Plasma Exchange (TPE)

"Who, what, when, where, how?! **NOW?**!!"

Unidentified Nephrology Fellow at 2 am

Overview and Agenda

- Introduction--Drs. Bolan and Yuan
- TTP/HUS Guidelines: Dr. Bolan
- Paraproteinemia/Hyperviscosity: Dr. Ward
- Neurologic Indications: Dr. Coates
- A Word from the Blood Bank: Dr. Chaffin
- Grand Finale

Overview: TPE Process Action Team

- Convened in Autumn, 1997, in response to marked increase in TPE treatments, especially for TTP
- Goals:
  - Identify reasons for ↑ number TPE treatments
  - Quantify impact on hospital resources
  - Identify ways to improve inter-service coordination

Overview: TPE Process Action Team

- Members:
  - Medical Director, TPE/Dialysis Program
  - Critical Care Nursing Representative
  - Medical Director, Blood Bank
  - Technical Director, Blood Bank
  - Representatives from:
    - Hematology/Oncology
    - Neurology
    - Bone Marrow Transplant

Overview: TPE Process Action Team

- Findings/Recommendations
  - Increase in TPE treatments doubled in FY96-97, but declined to 10-15 monthly in late 1997
    - ? Overvigilant diagnosis
    - ? Prolonged TPE in uncertain cases
  - Unfunded mandate for dialysis nursing personnel--after loss of technologist
  - 3 sites for pheresis at WRAMC: Blood bank, BMT, Dialysis--with different missions, but similar hardware, disparate software.

Overview: TPE Process Action Team

- Findings/Recommendations
  - Presently, no guidelines for collaboration of referring and treating services.

Therefore--

  - Hematology, Nephrology, Neurology should develop simple, evidence based practice guidelines for diagnosis and therapy for most common diseases requiring TPE.

Overview: TPE Process Action Team

- Findings/Recommendations
  - Blood Utilization Committee (BUC) should review all records for new cases requiring TPE, based on standardized check-lists reflecting practice guidelines.
  - Nephrology and Neurology be represented on BUC.
  - TPE should be separate from collection procedures, but machines and maintenance contracts should be shared.

Overview:
TPE Process Action Team

"Plasmapheresis and dialysis are essential to transfusion medicine and medical operational readiness--we need to do them well at WRAMC."

C. Bolan

General Guidelines Divison of Labor

Dr. Erin Bohen

Medical Director, Dialysis and TPE

General Guidelines for Division of TPE Labor

- Referring SVC:
  - Determines the necessity, timing and prescription
  - Contacts the Nephrology SVC
  - Counsels the patient in the context of the disease
  - Writes counseling and therapeutic plan note (staff)
  - Contacts Nephrology SVC for changes in plan
  - Assesses response to therapy
  - Attends scheduled, documented TPE “Progress” meetings
  - Participates in case review and divisional QA/QI

General Guidelines for Division of TPE Labor

- Nephrology SVC:
  - Evaluates the patient for TPE procedure
  - Discusses with referring SVC TPE RX and endpoints
  - Counsels the patient in the context of the procedure
  - Writes counseling and therapeutic plan note (staff)
  - Obtains vascular access
  - Writes TPE prescription
  - Coordinates with Blood Bank, Pharmacy, and Nursing

General Guidelines for Division of TPE Labor

- Nephrology SVC (continued):
  - Follows patient for complications
  - Writes procedure note after each procedure
  - Makes recommendations to referring SVC about drug dosage adjustments and TPE frequency
  - Attends scheduled, documented TPE "Progress" meetings
  - Participates in case review and divisional QA/QI

TTP/HUS Guidelines 1998

Dr. Charles Bolan
Hematology SVC

TTP/HUS Guidelines

- Timeline
  - Spring 1996- Fall of 1997; multiple consults for TPE for presumed TTP. 30 TPE tx's being done/month. Issues of coordination, management and responsibility evolve.
  - Fall 1997; Plasma Therapy Workshop at Army Regional ACP Meeting (Reston, VA). Expert panel: Drs. Barbara Alving, William Bell, James George, and Thomas Reid.

TTP/HUS Guidelines

- Timeline
  - Fall 1997; ACP Associate Presentation by Dr. Joseph Flynn at Army Regional ACP Meeting (Reston, VA). WRAMC experience with TPE for TTP. 9 patients treated over past year. 6 deaths. Thousands of units of FFP and PRBCs expended.
  - Late 1997. WRAMC Process Action Team convened, with findings presented Spring 1998.

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Plasmapheresis and Paraprotein-Related Hyperviscosity

WRAMC Practice Guidelines 1998

Waldenstrom's can have…

- Cytopenias from BM infiltration **
- Hyperviscosity from Ig M**
- Cryoglobulinemia
- Cold agglutinin syndrome
- Peripheral neuropathy
- Amyloidosis
- Nephrotic syndrome

Waldenstrom's Macroglobulinemia

- Clonal low-grade lymphoproliferative disorder
- Elderly age
- Adenopathy (20%); hepatosplenomegaly (40%) in minority
- Lymphoplasmacytic cells, pan-B markers (CD19, CD20 but neg CD10 [vs FL] and neg CD5/CD23 [vs CLL])

Multiple Myeloma

- Clonal plasma cell disorder
- Median age 68-70
- Various syndromes: overt, indolent, smoldering
- Anemia, bone complications, renal insufficiency, hypercalcemia
- Hyperviscosity rare

MULTIPLE MYELOMA

Major Criteria

Plasmacytoma on tissue biopsy

Bone marrow plasmacytosis with >30% plasma cells

Monoclonal globulin spike on serum electrophoresis exceeding 3.5 g/dL for G peaks or 2 g/dL for A peaks, ≥1 g/24 h of κ- or λ-light chain excretion on urine electrophoresis in the presence of amyloidosis

Minor Criteria

Bone marrow plasmacytosis 10% to 30% plasma cells

Monoclonal globulin spike present but less than the level defined above

Lytic bone lesions

Residual normal IgM <50 mg/dL, IgA < 100 mg/dL, or IgG <600 mg/dL

Diagnosis is confirmed when any of the following features are documented in symptomatic patients with clearly progressive disease. The diagnosis of myeloma requires a minimum of one major + one minor criterion or three minor criteria that must include a + b, i.e.:

I + b, I + c, I + d (I + a not sufficient)
II + b, II + c, II + d
III + a, III + c, III + d
a + b + c, a + b + d

Diagnosis of Paraprotein-Related Hyperviscosity

- Non-specific clinical syndrome
- Congruent lab data
- Exclude alternative explanations (e.g., lab errors)

Clinical Manifestations of Hyperviscosity

- Fatigue
- Dizziness
- Blurred Vision
- Easy bruising
- Mucosal bleeding
- Headache
- Mental status changes
- Eye: dilated sausage-shaped retinal veins, hemorrhages, papilledema
- Elevated blood pressure
- Volume overload

Clinical Manifestations of Hyperviscosity: Lab

- Anemia (usu dilutional)
- Elevated total protein
- Increased Total protein:albumen ratio
- Viscosity gen $\geq$ 3.0 Centistroke

HYPERVISCOSITY

- WALDENSTRO M'S
- IG M usu > 3 g/dl (80% in plasma)
- Plasmapheresis effective as single Rx

- MYELOMA
- IG A > 6 g/dl
- IG G > 10 g/dl
- Several (2-3) phereses needed

Hyperviscosity: Treatment

- **Indication for emergent therapy: symptomatic hyperviscosity with congruent lab data**
- **Consideration for pheresis: paraproteinemia without symptomatic hyperviscosity (e.g, neuropathy, cold agglutinin syndrome, etc)**
- **Expeditious systemic Rx**

Plasmapheresis

- **Volume: 1 - 1.5 volumes**
- **Replacement fluid: albumen and saline (individualized: ? partial plasma replacement if bleeding diathesis)**
- **End Points: plasma viscosity/serum paraprotein levels; symptoms ascribable to hyperviscosity.**
- **Frequency: 1 (WM) to 2 or 3 (MM)**

Hematology-Oncology Initial Responsibilities I

- **Confirm dx of WM / MM and hyperviscosity**
- **Attending note in chart before pheresis: reflects diagnosis, discussion of treatment with patient (plasmapheresis as treatment of choice), patient counseling**

Hematology-Oncology Initial Responsibilities II

- Commo/Coord with nephrology staff; agree on duration of treatments (1-3 usu)
- Writes pheresis plan (#, vol, freq, end points); reviewed with nephrology

Hematology-Oncology Initial Responsibilities III

- Begin therapy ASAP once dx established: goal -- within hours
- Daily monitoring of CBC, chemistries, viscosity, Ig levels, Coord rapid turnaround with DPALS during period of pheresis

Hematology-Oncology Initial Responsibilities IV

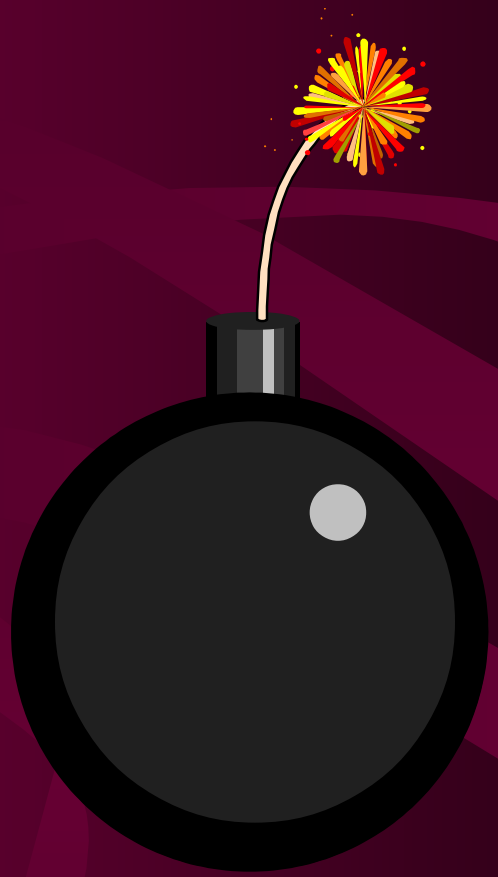
- **Daily assessment of need for further therapy by staff of heme and nephrology service: decision documented in daily notes by each service. Coord with nephrology service**
- **Begins systemic therapy ASAP: goal --within 24 hrs of confirming diagnosis**

Nephrology Responsibilities

- As for TPE except no expectation of weekly meeting

Summary

- **Hyperviscosity: Waldenstrom's and rarely Myeloma**
- **Nonspecific symptoms with elevated viscosity**
- **Symptomatic with congruent labs**
- **Plasmapheresis ASAP**



Neurological Indications for TPE 1998

Dr. Michael Coates
Dept of Neurology

Established Indications

- Guillian Barre Syndrome
- Chronic Demyelinating Inflammatory Polyneuropathy
- Myasthenia Gravis

Guillian Barre Syndrome

- Ascending weakness, acute onset, progressive over days to weeks, motor>>sensory, hyporeflexia
- Often follows an infectious or inflammatory illness
- Can be associated with autonomic instability

Guillian Barre Syndrome

- CSF shows normal glucose, increased protein (often >100) and no more than a slight increase in cells (all mononuclear, <10)
- EMG/NCV shows a pattern of demyelination (slow conduction velocity)

Guillian Barre Syndrome

- The mechanism of Guillian Barre Syndrome remains unclear however it involves an immune mediated destruction of the myelin in the peripheral nervous system. IgG and IgM against tubulin and GM1 are found.
- Unlike many immune mediated disorders, steroids are not effective

Guillian Barre Syndrome Indications for TPE

- Declining respiratory function, generally measured by FVC (declining from baseline)
- Decline in ambulation

Guillian Barre Syndrome

- Current AAN Guidelines suggest an exchange of 200-250 ml/kg total over 5 sessions (40-50 ml/kg/tx) or 1 to 1 and 1/2 plasma volumes per session for five sessions. Patients almost always receive only one course of treatment. Treatment should be initiated within 24 hours.
- IVIG is an acceptable alternative. The decision as to which to use is based on availability and rate of clinical decline.

Chronic Demyelinating Inflammatory Polyneuropathy

- Weakness with minimal sensory disturbance, hyporeflexia
- The course is chronic or relapsing (weeks to months)

Chronic Demyelinating Inflammatory Polyneuropathy

- CSF shows normal glucose, increased protein (often >100) and no more than a slight increase in cells (all mononuclear, <10)
- EMG/NCV shows a pattern of demyelination (slow conduction velocity)

Chronic Demyelinating Inflammatory Polyneuropathy

- The mechanism of CDIP remains unclear however it involves an immune mediated destruction of the myelin in the peripheral nervous system. IgG and IgM against tubulin are found.

Chronic Demyelinating Inflammatory Polyneuropathy

- The standard treatment is to start prednisone at 60 mg/day and to gradually taper over several months. Most patients require azathioprine in addition to steroids.
- Failure of oral medications is the usual indication for IVIG or TPE. There are no criteria for one therapy over the other. The decision is usually based on availability and specific patient factors

Chronic Demyelinating Inflammatory Polyneuropathy

- TPE guidelines for CDIP are similar to those of Guillian Barre Syndrome. Respiratory failure is rarely a problem with CDIP. Therefore TPE usually does not need to be immediately available.
- Some refractory patients will need “maintenance” exchanges. The interval for periodic exchanges varies from one to three months

Myasthenia Gravis

- Fluctuating weakness, especially of the cranial muscles and the muscles of respiration. Diplopia and ptosis are probably the most common presentations. Some patients will have symptoms limited to the eyes
- Sensory exam and reflexes are normal
- Some patients have an associated thymoma which can be detected by chest CT.

Myasthenia Gravis

- Tensilon test: IV administration of edrophonium (anticholinesterase inhibitor)
- REPSTIM: 10% decrement at 3-4 HZ
- Serum antibodies: present in over 90% of patients with generalized myasthenia

Myasthenia Gravis

- Defect in neuromuscular transmission.
- Due to antibodies (IgG) directed against the Ach receptors on the post-synaptic membrane.

Myasthenia Gravis

- Usual treatment consists of an anticholinesterase inhibitor (pyridostigmine) often accompanied by immune suppression with a combination of prednisone and azathioprine.
- Thymectomy is indicated for any patient with a thymoma as well as all patients with generalized myasthenia who are below the age of 60.

Myasthenia Gravis

- The indications for TPE in myasthenia are 1) myasthenic crisis manifested by severe weakness and often respiratory failure and 2) prior to a thymectomy in order to allow for less ventilator dependant time.
- For myasthenic crisis TPE should be available within 24 hours

Myasthenia Gravis

- There are multiple case reports describing successful treatment of myasthenia gravis with IVIG. The results of prospective, controlled studies are not available.
- IVIG is not yet an established treatment for myasthenia gravis.

Other Possible Neurological Indications for TPE Include

- Polyneuropathy associated with MGUS
- Eaton Lambert Syndrome
- Multiple Sclerosis
- Refsum’s Disease
- Acute Disseminated Encephalomyelitis
- Stiff Person Syndrome
- Neuromyotonia
- Cryogobulinemia
- CNS Lupus

Replacement Fluids

D. Joe Chaffin, MD

Medical Director, Blood Services

Apheresis Procedures in General

- Crystalloids
- Albumin and other colloids
- Plasma Products
  - Fresh Frozen Plasma (FFP)
  - Solvent-Detergent Treated Plasma (SDP)
  - Cryo-reduced Plasma

Comparison

SOLUTION	ADVANTAGES	DISADVANTAGES
Crystalloids	1. Low cost 2. No hepatitis risk	1. Hypo-oncotic 2. No coag factors or Igs
Colloids	1. Iso-oncotic 2. No hepatitis risk	1. High cost 2. No coag factors or Igs 3. dec BP with PPF
Plasma	1. Coag factors, Igs, complement	1. Infectious risk 2. Citrate load 3. ABO issues 4. Allergic rxns

An Effective Approach

- Most Diseases
  - Consider beginning with crystalloid replacement
    - Requires more volume (2-3 X that removed)
  - If so, switch to colloid at around 1/2 PV
  - Monitor coagulation tests to judge need for supplemental or replacement FFP

Coagulation Effect

- A one volume exchange may decrease fibrinogen as much as 75-80%!
  - Effect may last up to 4 days
- Other factors are much less affected
  - Other factors return to normal within 24 hours
- Platelets decrease 25-30% with procedure
  - Effect may last several days

Bottom Line

- With most diseases, the success of the procedure is really not dependent on the replacement fluid used.
- The exception, of course, is…..

TTP; A Different Ballgame!

- Replacement choices
  - Fresh Frozen Plasma
  - Cryo-reduced Plasma
  - Solvent/Detergent-treated Plasma (New)

FFP for TTP

- Replaces coag factors lost
- Replaces “bad plasma” with “good plasma”
- Is iso-oncotic
- Consider citrate effect
  - Ionized calcium
  - No systemic anticoagulation

Cryo-reduced Plasma for TTP

- Take FFP and make cryoprecipitate
  - Lose vWF, F VIII, Fibrinogen, F XIII
- Residual product may give less of what causes the problem in TTP
- Variably proven results
- Consider when FFP replacement not effective

Solvent/Detergent-Treated Plasma

- Approved in May 1998
- Marketed by Red Cross
  - approximately 3x as expensive as FFP
- Pooled product (2500 donors)
- Treated with solvent/detergent to remove enveloped viruses
- Also removes large vWF multimers

SDP and TTP

- Initial study
  - 26 patients
  - No differences in survival, remissions, or relapses between FFP and SDP group
- More study needed

Questions

Click here to take online quiz on this lecture